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Older age at first tuberculosis diagnosis is associated with tuberculosis recurrence in HIV-negative persons

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Summary

Setting: Tuberculosis clinic in Durban, South Africa

Objective: To assess factors associated with tuberculosis recurrence among HIV-seronegative adults and children

Design: We conducted a retrospective longitudinal study from January 2000 – December 2012. We defined recurrence as a tuberculosis episode occurring within the study period after treatment completion or cure of a prior episode. We used a multivariable Poisson regression model to assess factors associated with number of recurrences among HIV-seronegative patients.

Results: Among 17,941 patients with known HIV status, 3,653 (20%) were HIV-seronegative. Of the latter, 235 (6%) had one recurrence, 21 (1%) had two recurrences, and 4 (0.1%) had three recurrences. Median follow-up time from end of first episode treatment was 3.0 years (Interquartile Range 1.9, 4.2). Age at first tuberculosis episode was significantly associated with number of tuberculosis recurrences; younger patients had the lowest rate of recurrences, with steady increase in rates until age 40 years, after which rates remained stable.

Conclusions: Tuberculosis recurrence rates among HIV-seronegative patients were higher at increased age at first tuberculosis episode. Further translational studies are needed to clarify

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factors that drive multiple tuberculosis recurrences in older age, including impaired immunity, with potential implications for tuberculosis vaccines.

Keywords

Immunosenescence; Reinfection; Relapse

INTRODUCTION

Despite the availability of curative treatment, tuberculosis is the leading cause of death globally due to a single infectious pathogen.^{1,2} After completing treatment for tuberculosis, individuals can have recurrent tuberculosis disease, which can be due to relapse of previous *Mycobacterium tuberculosis* infection or exogenous reinfection.³ Reinfection comprises over half of recurrent tuberculosis cases in some high burden settings.⁴

Infection with human immunodeficiency virus (HIV) is associated with increased risk of recurrent tuberculosis, and in particular, increased risk of reinfection.^{5–10} Rates of tuberculosis recurrence can exceed those of new tuberculosis disease, both among HIV-seropositive and –seronegative individuals, in HIV and tuberculosis high burden settings.^{5,11} The increased risk of tuberculosis recurrence among persons living with HIV is attributed to impaired immunity, but little is known about factors influencing recurrence in HIV-seronegative persons.¹²

A study of South African gold miners showed that HIV-seronegative individuals who had more than one previous tuberculosis episode were more likely to have tuberculosis recurrence than those with only one previous episode.⁵ Little else is known about factors associated with multiple tuberculosis recurrences in the same individual. Similarly, there are few studies of tuberculosis recurrences among HIV-seronegative children.^{13,14} A better understanding of individuals with multiple recurrences of tuberculosis may provide important insights about protective immunity to tuberculosis critical for vaccine development, and for treatment and follow-up strategies.

In this study we used data from a large, urban tuberculosis clinic in South Africa to assess factors associated with tuberculosis recurrence among HIV-seronegative adults and children.

METHODS

We performed a retrospective longitudinal study of tuberculosis patients seen at the Prince Cyril Zulu Communicable Diseases Clinic (PCZCDC) in Durban, South Africa. The PCZCDC is an urban, municipal primary health care facility that provides focused tuberculosis care. The clinic had an electronic medical record designed for routine patient care starting in 1997. We included all new tuberculosis cases with known HIV serostatus whose first recorded tuberculosis care occurred between January 1, 2000 and December 31, 2012, and who had no previous history of tuberculosis. Follow-up was through December 31, 2013. We excluded patients who had resistance to isoniazid or rifampicin at first database entry. Analyses focused on HIV-seronegative patients, but we included HIV-seropositive patients in some analyses for comparison purposes. The University of

KwaZulu-Natal Biomedical Research Ethics Committee and the Vanderbilt University Medical Center Institutional Review Board approved the study with a waiver for informed consent.

Patients were treated according to local guidelines at the time.¹⁵ New drug-susceptible tuberculosis patients received isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) for two months (2HREZ) followed by 4HR. The retreatment regimen for persons who developed recurrent tuberculosis included: streptomycin (S) added to HREZ for the first two months (2SHREZ), then 1HREZ/5HRE. Patients with extrapulmonary tuberculosis received at least 9 months of treatment, and those with tuberculosis meningitis at least 12 months of treatment.

Our primary study outcome was tuberculosis recurrence, defined as a new tuberculosis episode occurring after cure or treatment completion of a prior tuberculosis episode during the study period. Treatment outcomes for each episode were recorded by clinicians at PCZCDC and based on World Health Organization (WHO) definitions at the time.¹⁶ Individual pharmacy records were not routinely captured in the electronic database. Therefore, to derive treatment completion date and the start of eligibility for tuberculosis recurrence,¹⁷ we used standard treatment practices to determine anticipated treatment durations: 180 days (new, drug-susceptible); 240 days (retreatment, drug-susceptible); 720 days (retreatment, isoniazid and rifampicin resistant); 360 days (meningitis); and 270 days (all other extrapulmonary). We calculated days to tuberculosis recurrence as the estimated treatment completion date of the prior episode to the treatment start date of the recurrent episode.

Each recurrent episode was determined based on cure or treatment completion of the previous episode. Follow-up time at-risk for recurrence was time from treatment completion until December 31, 2013, minus any treatment intervals due to recurrence. We plotted time to recurrence according to number of recurrence using Kaplan-Meier estimates.

We used the chi squared test for categorical variables and the Kruskal-Wallis test for continuous variables. We used the clinical database to determine variables at the time of first tuberculosis diagnosis: age, sex, race, culture and smear status, tobacco smoking status, and chest X-ray (CXR) findings as reported for clinical care of cavitary disease (yes/no) and any abnormalities in both left and right lung fields (bilateral disease; including, but not limited to miliary disease). We used multivariable Poisson regression models to evaluate factors associated with tuberculosis recurrences and to account for variable follow-up time for each patient. To account for patients who had multiple recurrences, we used a count variable with total number of recurrences for each patient as the dependent variable. Models used robust (sandwich) variance estimation.¹⁸ We included age in our models using restricted cubic splines with 3 knots to allow for non-linear associations;¹⁹ a Wald test assessed whether age was predictive of recurrence. We used follow-up time as an offset variable. To determine differences in risk factor associations for tuberculosis recurrences between HIV-seronegative and HIV-seropositive patients we fit models with interaction terms between HIV serostatus and other variables.

We used Stata, version 12.1 (Stata Corporation, College Station, TX, USA) for all analyses. P values were two-sided and $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, 17,941 new tuberculosis patients (adults and children) with known HIV status were treated at the study clinic, of whom 3,653 (20%) were HIV-seronegative. Among HIV-seronegative patients, 260 (7%) had at least one tuberculosis recurrence; 235 had a single tuberculosis recurrence, 21 had two recurrent episodes, and 4 had three recurrences. Median at-risk follow-up time was 3.0 years (IQR 1.9, 4.2).

Table 1 compares factors present at the time of first tuberculosis episode for HIV-seronegative patients divided into 3 groups: those who had more than one recurrence, those who had only one recurrence, and those who did not have any recurrences. Patients with more than one recurrence were significantly older at the time of first tuberculosis episode than patients who only had one recurrence and those without any recurrences. At first tuberculosis episode, 2,064 (57%) patients had smear or culture positive disease.

Of 3,653 HIV-seronegative patients, 624 (17%) were children (<18 years) at the time of first tuberculosis episode. Twenty-seven (4%) children had at least one recurrence; 26 had one recurrence and 1 had two recurrences.

Among all 260 patients who had 1 tuberculosis recurrence, median time to first tuberculosis recurrence was 3.2 years (Interquartile range [IQR] 1.7, 6.1). Furthermore, 39 (15%) patients had recurrence within 1 year, 37 (14%) had recurrence between 1 and 2 years, and 184 (71%) had recurrence >2 years after estimated treatment completion. Time to additional recurrences is shown in Figure 1.

Of 984 patients who had drug susceptibility tests performed during follow-up, 26 patients developed resistance to any drug (26 developed resistance to isoniazid, 22 to rifampicin, 4 to ethambutol, 13 to streptomycin, 5 to kanamycin, 4 to fluoroquinolones. Fifteen patients who developed resistance to any drug had 1 tuberculosis recurrence.

We used a regression model to assess factors associated with number of tuberculosis recurrences among 3,185 (87%) HIV-seronegative patients with complete data. Excluded patients were significantly more likely to be older and male with smear positive, pulmonary tuberculosis than patients included in the model. Age at first TB episode was strongly associated with TB recurrence ($P < 0.001$) and in a non-linear manner ($P < 0.001$; test of non-linearity). The lowest rates of tuberculosis recurrence occurred among the youngest patients (Table 2 and Figure 2). The rate of tuberculosis increased with age until about 40 years, after which the rate of recurrence remained about the same, though confidence intervals for the association widened. Male sex and bilateral lung disease on CXR at first tuberculosis episode were associated with number of tuberculosis recurrences (Table 2). We used a similar model to evaluate factors associated with tuberculosis recurrences among 13,080 (92%) HIV-seropositive patients with complete data (Table 3, Figure 3). Associations between male sex and pulmonary disease with increasing numbers of recurrences were

similar between HIV-seropositive and HIV-seronegative patients ($P>0.15$, test for interaction for both).

DISCUSSION

Our aim was to determine factors associated with recurrent tuberculosis in HIV-seronegative tuberculosis patients from a region with a high force of tuberculosis infection. We found that age at first tuberculosis episode was associated with the number of tuberculosis recurrences. Specifically, patients who had more recurrences were older at their first tuberculosis episode than patients who had a single recurrence, who in turn were older than patients without recurrences. In an adjusted, multivariable model, rates of tuberculosis recurrence were lower at younger ages and increased until 40 years of age after which they remained stable, albeit with widened confidence intervals.

It is conceivable that greater environmental exposure to tuberculosis, the presence of unmeasured co-morbidities, more alcohol use, differences in socioeconomic conditions or more stable follow up (potential differences in mobility for employment, family reasons, or other motivations) occurred in older patients, which could explain why age at first tuberculosis episode was associated with increasing number of recurrences. Due to the retrospective design we were unable to adjust for all of these factors; further studies are required to establish which factors drive the association between age and recurrence.

The association between age and recurrence could be influenced by immunological factors. Premature immunosenescence, which has similar immunological characteristics to those observed in HIV infection, has been described in HIV-seronegative individuals.^{20,21} Chronic psychological stress and persistent viral infections such as human cytomegalovirus have been associated with premature immunosenescence; these and other environmental factors may be broadly present in resource-limited settings.^{22,23} Both mouse models and computational modeling of the immune response to tuberculosis infection incorporating immune system aging effects suggest that factors such as impaired recruitment of protective CD4⁺ T cells could contribute to increased tuberculosis susceptibility.^{24,25} We compared age of first active tuberculosis disease rather than age of primary infection with *M. tuberculosis*, and more research is needed to determine if there are age-related immune defects that increase the risk of recurrent tuberculosis.

Tuberculosis recurrence can be due to either relapse or exogenous reinfection, which are clinically indistinguishable. Since sputum samples were not routinely stored, we did not have *M. tuberculosis* isolates available for genotypic analysis to distinguish between relapse and reinfection. Not surprisingly, as the incidence of tuberculosis and risk of infection increase, so does the relative contribution of reinfection to overall recurrence.²⁶ In one study in South Africa, relapse occurred significantly earlier than reinfection, with the majority of relapses occurring in the first year.⁴ We found that 15% of all first recurrences occurred within the first year (median time of 3.2 years to first recurrence). Median times to second and third recurrence were shorter (3.0 and 1.7 years, respectively). These findings suggest that reinfection (and therefore concerns about patient susceptibility to tuberculosis rather than adequacy of previous treatment) also played a large role in tuberculosis recurrences in

HIV-seronegative patients in our setting. We do not have adherence data, but because the timing of recurrence was late (more consistent with reinfection) we do not believe differences in adherence explain the risk of recurrence across different age groups.

In addition to age we found that male sex was associated with an increasing number of tuberculosis recurrences. One previous study has shown a similar gender association with male sex and tuberculosis reactivation.²⁷ Males have a higher incidence¹ and prevalence of tuberculosis²⁸ and worse treatment outcomes.²⁹ Despite variation in health seeking behavior, adherence to therapy, occupation, smoking and other behavioral traits there is a growing consensus that biological factors also contribute to these gender differences.^{30,31} Our association between male sex and recurrent tuberculosis could also be a reflection of sex differences in the immunological control of tuberculosis.

Multiple recurrences of tuberculosis in HIV-seronegative individuals have been previously described.⁵ Patients who have had tuberculosis before have a higher risk of recurrent infection than the baseline incidence of tuberculosis in the population.¹¹ Individuals with multiple recurrences pose a particular challenge for the development of a tuberculosis vaccine. If as our study suggests, these are at least in part due to reinfection, then these individuals fail to develop protective immunity despite multiple infections with *M. tuberculosis*. Further studies elucidating the immune mechanisms at play and the role of host genetic susceptibility in these patients could provide important insights for the successful development of a tuberculosis vaccine, and persons who may not benefit from vaccination.^{12,32}

Less is known about recurrent tuberculosis in children, but one study reported that among 56 HIV-seropositive children, 9 had tuberculosis recurrence, 2 of whom had a second recurrence.¹⁴ In our study, we found that a higher proportion of adults had tuberculosis recurrences than children. We also identified 1 HIV-seronegative child with multiple recurrences. Further characterization of immune mechanisms leading to decreased risk of tuberculosis recurrence in children may provide valuable insights into vaccine development and strategies to prevent recurrent disease in children.

Our study has several limitations, primarily related to the retrospective use of programmatic data. Individual tuberculosis treatment records were not available in the electronic data, so we used the length of standard treatment regimens in our analyses. Therefore, we were unable to account for treatment interruptions, patient non-adherence, or individual variation in length of treatment. In order for any additional tuberculosis episodes to be considered as recurrences, however, patients had to have documented cure or treatment completion of preceding episodes. Patients with treatment completion did not have microbiological confirmation of cure, which is also a limitation, but completion of 6-months of therapy for drug-susceptible tuberculosis is known to result in very high cure rates. Among all patients who were seen at PCZCDC, a substantial percentage moved, transferred, or was lost to follow up. It is possible that some patients with recurrence received treatment at other facilities. These factors probably contributed to overestimation of follow-up time, and underestimation of the absolute risk of recurrence and perhaps biasing our analyses in other ways. This highlights the urgent need for integrated data systems among tuberculosis treatment

facilities. Additionally, a substantial percentage of patients (43%) did not have smear or culture confirmation of tuberculosis at the first episode. The high proportion of clinically-diagnosed tuberculosis could cause bias by inclusion of false positive cases. Finally, we relied on programmatic data to inform HIV serostatus of patients. Some patients who were HIV-seronegative at the time of an earlier tuberculosis episode could have become infected with HIV thereafter.

The main strength of our study was the large study population at a single site in a high HIV and tuberculosis incidence setting. Given the overall study limitations, we likely underestimated tuberculosis recurrence, but still demonstrated that recurrence was not limited to a single occurrence in a considerable number of individuals. After adjusting for multiple factors, we demonstrated that compared to someone age 20 years, tuberculosis recurrence risk was increased in persons age 30 or higher (and particularly those age 40 or higher) and decreased in those age 5 or 10. Additional studies may help clarify underlying immune correlates in HIV-seronegative patients with multiple tuberculosis recurrences, with implications for tuberculosis vaccine development.

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Figure 1.
Comparison of time to tuberculosis recurrence by number of tuberculosis recurrences among HIV-seronegative patients.

Figure 2.

Rate of TB recurrence per year among HIV-seronegative patients according to age using a restricted cubic spline model for age. All other covariates were fixed at representative values at the time of first tuberculosis episode (male, pulmonary disease, non-cavitary disease on chest X-ray, unilateral lung disease on chest X-ray, non-smoker). Boundaries of shadow region denote 95% confidence intervals.

Figure 3.

Rate of TB recurrence per year among HIV-seropositive patients according to age using a restricted cubic spline model. All other covariates were fixed at representative values at the time of first tuberculosis episode (male, pulmonary disease, non-cavitary disease on chest X-ray, unilateral lung disease on chest X-ray, non-smoker). Boundaries of shadow region denote 95% confidence intervals.

Table 1.

Comparison of demographic and clinical features of HIV-seronegative patients with multiple, single, and no TB recurrences.

Demographic and Clinical Characteristics at First TB episode	> 1 Recurrence N=25 [*]	1 Recurrence N= 235 [*]	No Recurrence N= 3,393 [*]	P value Overall
Age, median (IQR) years	41 (36, 45)	30 (22, 41)	27 (21, 36)	<0.001
Male sex	21 (84)	158 (67)	2,019 (60)	0.003
Race [‡]				<0.001
Black	22 (88)	201 (86)	3,219 (95)	
Asian	0	16 (7)	99 (3)	
Coloured	3 (12)	14 (6)	49 (1)	
White	0	4 (2)	26 (1)	
Culture-confirmed	5/6 (83)	51/85 (60)	886/1,271 (70)	0.13
Smear-positive	21/25 (84)	162/222 (73)	1,522/2,663 (57)	<0.001
Extrapulmonary TB	0	32/235 (14)	617/3,393 (18)	0.01
Cavitary disease on CXR	9/24 (38)	94/232 (41)	716/2,959 (24)	<0.001
Bilateral disease on CXR	10/24 (42)	121/232 (52)	919/2,959 (31)	<0.001
Smoker	8 (32)	44 (19)	467 (14)	0.004

HIV: human immunodeficiency virus; TB: tuberculosis; IQR: interquartile range; CXR: chest X-ray

Numbers in brackets correspond to percentage, except for age, which corresponds to IQR.

^{*} Column totals unless otherwise indicated. Missing data were excluded from calculations.

[‡] Race categories as recorded in the patient record.

Table 2.

Multivariable analysis demonstrating association between factors and TB recurrences among HIV-seronegative patients.*

Demographic and Clinical Characteristics at First TB episode	Incidence Rate Ratio (95% Confidence Interval)	P value
Age (years)		<0.001 [‡]
5	0.40 (0.29, 0.55)	
10	0.55 (0.45, 0.68)	
20 (reference)	1	
30	1.46 (1.29, 1.65)	
40	1.65 (1.38, 1.98)	
50	1.64 (1.27, 2.12)	
60	1.60 (1.11, 2.30)	
70	1.55 (0.96, 2.51)	
Male sex	1.37 (1.06, 1.78)	0.02
Extrapulmonary TB	0.71 (0.49, 1.03)	0.07
Cavitary disease on CXR	1.27 (1.00, 1.63)	0.05
Bilateral disease on CXR	1.37 (1.08, 1.73)	0.01
Smokes tobacco	0.89 (0.67, 1.19)	0.43

TB: tuberculosis; HIV: human immunodeficiency virus; CXR: chest X-ray

* Poisson regression model used 3,185 HIV-seronegative patients with complete data for all fields. All variables included in the model are shown in the table.

[‡]Wald test

Table 3.

Multivariable analysis between factors and TB recurrences among HIV-seropositive patients.*

Demographic and Clinical Characteristics at First TB episode	Incidence Rate Ratio (95% Confidence Interval)	P value
Age (years)		<0.001 [†]
5	0.82 (0.75, 0.90)	
10	0.88 (0.83, 0.93)	
20 (reference)	1	
30	1.11 (1.05, 1.17)	
40	1.00 (0.92, 1.08)	
50	0.78 (0.67, 0.91)	
60	0.61 (0.48, 0.78)	
70	0.48 (0.34, 0.67)	
Male sex	1.30 (1.19, 1.41)	<0.001
Extrapulmonary TB	0.83 (0.75, 0.91)	<0.001
Cavitary disease on CXR	1.46 (1.32, 1.62)	<0.001
Bilateral disease on CXR	0.96 (0.88, 1.04)	0.32
Smokes tobacco	1.02 (0.90, 1.17)	0.72

TB: tuberculosis; HIV: human immunodeficiency virus; CXR: chest X-ray

* Poisson model used 13,080 HIV-seropositive patients with complete data for all fields. All variables included in the model are shown in the table.

[†]Wald test